

Amendment to the specification:

Insert the paper copy of the Sequence Listing filed herewith following the Drawings.

Please amend the paragraph beginning at page 23, line 8, as follows:

Fig. 2 is a panel of graphs depicting T cell responses to HPV type 16, HPV type 18, HPV type 6, and HPV type 11 peptides (#1, SEQ ID NO:50; #2, SEQ ID NO:93; #3, SEQ ID NO:94; #4, SEQ ID NO:23; #5, SEQ ID NO:65; #6, SEQ ID NO:95; #7, SEQ ID NO:96; #8, SEQ ID NO:97; and #9, SEQ ID NO:98) following treatment of individuals with ZYC101a.

Please amend the paragraph beginning at page 15, line 24, as follows:

The polypeptide may optionally include a targeting signal. A targeting signal is a peptide which directs intracellular transport or secretion of a peptide to which it is attached. The targeting signal can be at the amino terminus, e.g., a signal sequence, or carboxy terminus, or within the hybrid polypeptide, so long as it functions in that site. A preferred targeting signal is the signal peptide of HLA-DR α : Met Ala Ile Ser Gly Val Pro Val Leu Gly Phe Phe Ile Ile Ala Val Leu Met Ser Ala Gln Glu Ser Trp Ala SEQ ID NO:92). The targeting signal may optionally be modified to introduce an amino acid substitution at the junction(s) between the targeting signal and the adjacent segment(s) to promote cleavage of the targeting sequence from the epitopes by, e.g., a signal peptidase.

Please amend the paragraph beginning at page 17, line 16, as follows:

The nucleic acid encoding a hybrid polypeptide can optionally contain any one or more of the segments AMFQDPQERPRKLPQLCTEL (SEQ ID NO:1), LLRREVYDFAFRDLCIVYRDGNPY (SEQ ID NO:2), KISEYRHYCYSLYGTTLEQQYNK (SEQ ID NO:3), TLHEYMLDLQPETTDLYSY (SEQ ID NO:4), QAEPDRAHYNIVTF (SEQ ID NO:5), LLMGTLGIVCPICSQKP (SEQ ID NO:6), RRPYKLPDLCTELNTSLQDIEITCVYCKTVLELTFEFAFK (SEQ ID NO:7), SVYGDTLEKLTNTGLYNLLIRCLRCQK (SEQ ID NO:8), KATLQDIVLHLEPQNEIPV

(SEQ ID NO:9), HTMLCMCKCEARI (SEQ ID NO:10), and AFQQLFLNTLSFVCPWC (SEQ ID NO:11).

Please amend the paragraph beginning at page 18, line 15, as follows:

In some embodiments of any of the methods or compositions described herein, the polypeptide is a hybrid polypeptide comprising at least one of the following segments of HPV strain 16 E6:

AMFQDPQERPRKLPQLCTEL (SEQ ID NO:1),
LLRREVYDFAFRDLCIVYRDGNPY (SEQ ID NO:2), or
KISEYRHYCYSLYGTTLEQQYNK (SEQ ID NO:3),
and at least one of the following segments of HPV strain 16 E7:
TLHEYMLDLQPETTDLYSY (SEQ ID NO:4),
QAEPDRAHYNIVTF (SEQ ID NO:5), or
LLMGTLGIVCPICSQKP (SEQ ID NO:6).

Please amend the paragraph beginning at page 19, line 1, as follows:

In some embodiments of any of the methods or compositions described herein, the polypeptide is a hybrid polypeptide comprising at least one of the following segments of HPV strain 16 E6:

AMFQDPQERPRKLPQLCTEL (SEQ ID NO:1),
LLRREVYDFAFRDLCIVYRDGNPY (SEQ ID NO:2), or
KISEYRHYCYSLYGTTLEQQYNK (SEQ ID NO:3);
at least one of the following segments of HPV strain 16 E7:
TLHEYMLDLQPETTDLYSY (SEQ ID NO:4),
QAEPDRAHYNIVTF (SEQ ID NO:5), or
LLMGTLGIVCPICSQKP (SEQ ID NO:6);
at least one of the following segments of HPV strain 18 E6:

RRPYKL PDLCTELNTSLQDIEITCVYCKTVLEL TEVFEFAFK (SEQ ID NO:7), or

SVYGDTLEKLTNTGLYNLLIRCLRCQK (SEQ ID NO:8),

and at least one of the following segments of HPV strain 18 E7:

KATLQDIVLHLEPQNEIPV (SEQ ID NO:9),

HTMLCMCKCEARI (SEQ ID NO:10), or

AFQQLFLNTLSFVCPWC (SEQ ID NO:11).

Please amend the paragraph beginning at page 19, line 18, as follows:

In some embodiments of any of the methods or compositions described herein, the polypeptide: (1) comprises the amino acid sequence

AMFQDPQERPRKLPQLCTELLLRREVYDFAFRDLCIVYRDGNPYKISEYRHYCYSLYGT
TLEQQYNKTLHEYMLDLQPETTDLYSYQAEPDRAHYNIVTFLLMGTLGIVCPICSQKPR
RPYKL PDLCTELNTSLQDIEITCVYCKTVLEL TEVFEFAFKSVYGDTLEKLTNTGLYNLLI
RCLRCQKKATLQDIVLHLEPQNEIPVHTMLCMCKCEARIAFQQLFLNTLSFVCPWC
(SEQ ID NO:12); (2) comprises the amino acid sequence

MAISGVPVLGFFHIAVLMSAQESWAAMFQDPQERPRKLPQLCTELLLRREVYDFAFRDL
CIVYRDGNPYKISEYRHYCYSLYGT TLEQQYNKTLHEYMLDLQPETTDLYSYQAEPDRA
HYNIVTFLLMGTLGIVCPICSQKPRRPYKL PDLCTELNTSLQDIEITCVYCKTVLEL TEVFE
FAFKSVYGDTLEKLTNTGLYNLLIRCLRCQKKATLQDIVLHLEPQNEIPVHTMLCMCK
CEARIAFQQLFLNTLSFVCPWC (SEQ ID NO:13); or (3) consists of the amino acid sequence
MAISGVPVLGFFHIAVLMSAQESWAAMFQDPQERPRKLPQLCTELLLRREVYDFAFRDL
CIVYRDGNPYKISEYRHYCYSLYGT TLEQQYNKTLHEYMLDLQPETTDLYSYQAEPDRA
HYNIVTFLLMGTLGIVCPICSQKPRRPYKL PDLCTELNTSLQDIEITCVYCKTVLEL TEVFE
FAFKSVYGDTLEKLTNTGLYNLLIRCLRCQKKATLQDIVLHLEPQNEIPVHTMLCMCK
CEARIAFQQLFLNTLSFVCPWC (SEQ ID NO:14).

Please amend the paragraph beginning at page 24, line 19, as follows:

A variety HPV peptide epitopes have been characterized using methods such as those described herein. Examples of specific HPV epitopes (e.g., HPV strain 16 and 18 E6 and E7 derived epitopes) are described in, e.g., U.S. Patent No. 6,183,746, WO 01/19408, U.S. Patent No. 6,037,135, WO 99/45954, WO 99/22338, and WO 97/33602, the content of which is incorporated herein by reference. Non-limiting examples of MHC class I-binding HPV peptides, one or more of which can be included in a polypeptide encoded by a nucleic acid described herein, include:

(1) ISEYRHYCY (SEQ ID NO:15), FQDPQERPR (SEQ ID NO:16), RREVDFAF (SEQ ID NO:17), TTLEQQYNK (SEQ ID NO:18), FQDPQERPRK (SEQ ID NO:19), ISEYRHYCYS (SEQ ID NO:20), KISEYRHYCY (SEQ ID NO:21), GTTLLEQQYNK (SEQ ID NO:22), KLPQLCTEL (SEQ ID NO:23), KISEYRHYC (SEQ ID NO:24), FAFRDLCIV (SEQ ID NO:25), YCYSIYGTTL (SEQ ID NO:26), SEYRHYCYSL (SEQ ID NO:27), AMFQDPQER (SEQ ID NO:28), LLRREVYDF (SEQ ID NO:29), IVYRDGNPY (SEQ ID NO:30), VYDFAFRDL (SEQ ID NO:31), CYSLYGTTL (SEQ ID NO:32), EYRHYCYSL (SEQ ID NO:33), KLPQLCTEL (SEQ ID NO:34), DPQERPRKL (SEQ ID NO:35), HYCYSLYGT (SEQ ID NO:36), DFAFRDLCI (SEQ ID NO:37), LYGTTLEQQY (SEQ ID NO:38), HYCYSLYGTT (SEQ ID NO:39), EVYDFAFRDL (SEQ ID NO:40), EYRHYCYSLY (SEQ ID NO:41), VYDFAFRDLC (SEQ ID NO:42) (HPV 16 E6 epitopes);

(2) QAEPDRAHY (SEQ ID NO:43), IVCPICSQK (SEQ ID NO:44), QPETTDLY (SEQ ID NO:45), QAEPDRAHYN (SEQ ID NO:46), DLQPETTDLY (SEQ ID NO:47), YMLDLQPET (SEQ ID NO:48), TLHEYMLDL (SEQ ID NO:49), LLMGTLGIV (SEQ ID NO:50), LMGTLGIVC (SEQ ID NO:51), MLDLQPETT (SEQ ID NO:52), TLGIVCPIC (SEQ ID NO:53), DLQPETTDL (SEQ ID NO:54), TLGIVCPI (SEQ ID NO:55), MLDLQPETT (SEQ ID NO:56), QPETTDLY (SEQ ID NO:57), LMGTLGIVC (SEQ ID NO:58), LQPETTDL (SEQ ID NO:59), TLHEYMLDL (SEQ ID NO:60), TLHEYML (SEQ ID NO:61), HYNIVTF (SEQ ID NO:62), and EPDRAHYNI (SEQ ID NO:63), (HPV 16 E7 epitopes);

(3) LTEVFEFK (SEQ ID NO:64), KLPDLCTEL (SEQ ID NO:65), GLYNLLIRC (SEQ ID NO:66), SLQDIEITC (SEQ ID NO:67), SLQDIEITCV (SEQ ID NO:68), LQDIEITCV (SEQ ID NO:69), KTVLELTEV (SEQ ID NO:70), ELTEVFIFA (SEQ ID NO:71),

KLTNTGLYNL (SEQ ID NO:72), LTNTGLYNL (SEQ ID NO:73), GLYNLLIRCL (SEQ ID NO:74), VLELTEVFEF (SEQ ID NO:75), SVYGDTLEK (SEQ ID NO:76), LLIRCLRCQK (SEQ ID NO:77), VYCKTVLEL (SEQ ID NO:78), VYGDTLEKL (SEQ ID NO:79), and LTNTGLYNLL (SEQ ID NO:80) (HPV 18 E6 epitopes); and

(4) HLEPQNEIPV (SEQ ID NO:81), TLQDIVLHL (SEQ ID NO:82), ATLQDIVLHL (SEQ ID NO:83), QLFLNTLSFV (SEQ ID NO:84), MLMCCKCEA (SEQ ID NO:85), CMCKCEARI (SEQ ID NO:86), FQQLFLNTL (SEQ ID NO:87), TLSFVCPWC (SEQ ID NO:88), HTMLCMCK (SEQ ID NO:89), QLFLNTLSF (SEQ ID NO:90), and AFQQLFLNTL (SEQ ID NO:91) (HPV 18 E7 epitopes).

Please amend the paragraph beginning at page 30, line 18, as follows:

An example of an ER-targeting sequence is the HLA-DR α leader sequence (MAISGVPVLGFFIIAVLMSAQESWA (SEQ ID NO:92)). The targeting sequence may include only a portion (e.g., at least ten amino acid residues) of this specified 25 residue sequence, or a slightly modified version of this sequence, provided that the portion or modified sequence is sufficient to cause targeting of the polypeptide to the ER.

Please amend the paragraph beginning at page 44, line 12, as follows:

A study with ZYC101a for the treatment of HSIL of the uterine cervix was performed as a Phase 2, multi-center, international, double-blind, placebo-controlled, trial. ZYC101a is a formulation comprised of plasmid DNA encapsulated in biodegradable poly (D,L-lactide-co-glycolide) (PLG) microparticles. The ZYC101a plasmid encodes a polypeptide that includes HPV 16 and 18 coding sequences and was optimized for increased immunogenicity by inclusion of immunogenic regions of HPV16 E6 and E7 proteins and HPV18 E6 and E7 proteins. The ZYC101a plasmid, which is described in detail in WO 01/19408, encodes a polypeptide having the following amino acid sequence:

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MAISGVPVLGFFIIAVLMSAQESWAAMFQDPQERPRKLPQLCTELLRREVYDFA
FRDLCIVYRDGNPYKISEYRHYCYSLYGTTLEQQYNKTLHEYMLDLQPETTDLYSYQAE
PDRAHYNIVTFLLMGTLGIVCPICSQKPRRPYKLPDLCTELNTSLQDIEITCVYCKTVLEL
TEVFEFAFKSVYGDTLEKLTNTGLYNLLIRCLRCQKKATLQDIVLHLEPQNEIPVHTMLC
MCCKCEARIAFQQLFLNTLSFVCPWC (SEQ ID NO:14).